REMARKS

Courtesies extended to Applicants' representative by Examiners DeWitty and Pryor during the personal interview held on November 21, 2002 are acknowledged with appreciation.

By the present communication, claims 32, 72, 75, 79, 80, 86 and 89-91 have been amended (and claims 68 and 69 cancelled without prejudice) to define Applicants' invention with greater particularity. No new matter is introduced by the subject amendments as all amended claim language is fully supported by the specification and original claims. These amendments are presented to address various informalities and inconsistencies in the claims.

In addition, new claims 94-121 are also submitted herewith to define Applicants' invention with greater particularity. These claims are also fully supported by the specification and original claims. APPENDIX A provided herewith provides a mark-up version of the amended claims showing the changes made by the present amendments.

Upon entry of the amendments submitted herewith, claims 29-35, 46-67 and 70-121 will remain pending. For the Examiner's convenience, a clean set of all pending claims as they will stand upon entry of the amendments submitted herewith is provided as APPENDIX B.

The rejection of claims 29-35, 46-51 and 66-85 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, is respectfully traversed. As discussed at the personal interview, taxanes are clearly disclosed in the present specification. The confusion appears to be the result of the present PTO file containing a copy of the application as originally filed, whereas Applicants were under the impression that the Substitute Specification submitted to the PCT during the international phase of this application would be the current operative document. In efforts to avoid any further confusion, Applicants submit herewith a Replacement Specification, which conforms to the Substitute Specification submitted

to the PCT during the international phase of this application. It will be observed that the term "taxane" appears at page 22, line 12 of this Replacement Specification (for the Examiner's reference, this term appears at page 20 of the original specification currently in the PTO files). Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

The rejection of claims 29-35 and 46-93 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-6, 17-18, 31-36 of U.S. Patent No. 6,096,331, is respectfully traversed. Without admitting the propriety of this rejection, in order to reduce the issues and expedite prosecution of this application, Applicants hereby submit a terminal disclaimer disclaiming the term of any patent to issue on the present application which would extend beyond the term of '331. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

In response to the assertion of newly cited art at the personal interview, Applicants respectfully disagree with the Examiner's assertion that patent abstracts US 5972992A, US 5977164A, US 6140359A, and US 6306894B read on the instant invention. These newly cited abstracts do not read on the instant invention, as claimed, for several reasons, e.g.,

- All of the cited abstracts are drawn to cremophor-containing (polyethoxylated castor oil) compositions, which are known to leach plasticizers from medical hardware.
- The Physicians Desk Reference (53rd Edition, 1999, p. 801, col. 1) teaches against the contact of undiluted Taxol with plasticized polyvinyl chloride (PVC) equipment used for infusion, to minimize patients exposure to DEHP (diethylexylphthalate), which may be leached from PVC infusion bags and tubing.
- PDR teaches storage of cremophor-containing (polyethoxylated castor oil) compositions in glass bottles and administration of such compositions using polyethylene lined administration sets for the prevention of leaching.
- Prior art teaches DEHP leaching in PVC administration sets due to cremophor. See, for example, the following papers (copies attached for the Examiner's convenience):

- Trissel, (Pharmacotherapy, 1997, (5 Pt2):133S-139S) teach paclitaxel formulations comprising Cremophor EL cause leaching of the plasticizer DEHP (diethylexylphtalate) from PVC-containing solution bags and administration sets and safe delivery of paclitaxel, using non-PVC containers and administration sets.
- Nuijen, et al., (Anticancer Drugs, 1999, 10(10):879-87), teach DEHP leaching in administration of aplidine containing cremophor, in administration sets made of PVC and teach safe administration in sets consisting of glass containers and PVC-free infusion tubing.

Accordingly, it is well known in the art that taxane compositions comprising cremophor cannot be "safely administered" in medical hardware made from materials containing extractable components. Therefore, the newly cited abstracts do not read on the instant invention as claimed because the instant invention is drawn to a taxane, (p. 24, line 30) that does not leach plasticizers, may be used in standard infusion tubing (p. 30, line 22) and thus, may be safely administered in medical hardware made from extractable components.

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any issues remain to be resolved in view of this communication, the Examiner is invited to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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ENCLOSURES: APPENDIX A
APPENDIX B
Abstract of Trissel, (Pharmacotherapy, 1997, (5 Pt2):133S-139S)
Abstract of Nuijen, et al., (Anticancer Drugs, 1999, 10(10):879-87)
Terminal Disclaimer
Replacement Specification

APPENDIX A

Markup version of amended claims:

32. (Twice amended) A method for the administration of a taxane to a human subject in need thereof, said method comprising systemically administering a complete dose of said taxane to said subject in a volume of less than 250 ml.

72. (Amended) An article of manufacture according to claim [~~74~~] 71, wherein said formulation is stable for at least 3 days.

75. (Amended) An article of manufacture according to claim [~~73~~] 74, wherein said liquid formulation of taxane is free of surfactants.

79. (Amended) The [~~composition~~] formulation of claim 46 wherein said [~~nonoparticles~~] nanoparticles have a mean particle size in the range of about 29 nm up to about 400 nm.

80. (Amended) The [~~composition~~] formulation of claim 46 wherein said dry powder formulation of taxane is suitable for the treatment of tumors in the brain or peritoneal cavity.

86. (Amended) [~~A drug~~] The formulation [~~according to~~] of claim 52 wherein said drug nanoparticles are contained within protein microparticles having a size of about 1-10 μm.

89. (Amended) The [~~composition~~] article of claim 88 wherein said drug formulation is a dry powder.

90. (Amended) The [~~composition~~] article of claim 88 wherein the drug formulation is a liquid.

91. (Amended) The **[~~composition~~]** article of claim 88 wherein said drug is hydrophobic.

APPENDIX B

Complete set of pending claims:

29. (Previously amended) A method for the administration of a taxane to a subject in need thereof, said method comprising systemically administering said taxane to said subject in a formulation that may be safely administered using medical hardware made from materials containing extractable components.

30. (Reiterated) A method according to claim 29, wherein said medical hardware is selected from the group consisting of tubing, catheters, infusion bags, bottles, and syringes.

31. (Previously amended) A method for the administration of a taxane to a subject in need thereof, said method comprising systemically administering said taxane to said subject in a formulation that may be safely administered without the use of an in-line filter.

32. (Twice amended) A method for the administration of a taxane to a human subject in need thereof, said method comprising systemically administering a complete dose of said taxane to said subject in a volume of less than 250 ml.

33. (Reiterated) A method according to claim 32, wherein said volume is less than 150 ml.

34. (Reiterated) A method according to claim 32, wherein said volume is less than 60 ml.

35. (Previously amended) A method for the administration of a taxane to a human subject in need thereof, said method comprising systemically administering said taxane to said subject at a rate between 6-30 $mg/m^2/min$ over an administration period of one hour or less.

46. (Previously amended) A dry powder formulation suitable for administration of a taxane to a human subject in need thereof upon reconstitution, wherein said formulation comprises taxane nanoparticles having a mean particle size in the range of about 10 nm up to about 8 μm, wherein said formulation is substantially free of surfactant.

47. (Previously amended) A formulation according to claim 46 wherein said formulation is lyophilized.

48. (Previously amended) A frozen formulation of a taxane suitable for administration of a taxane to a subject in need thereof upon thawing.

49. (Previously amended) A liquid formulation of a taxane suitable for administration to a human subject, said formulation comprising water and a taxane at a concentration of at least 2.0 mg/ml, wherein said formulation is stable for at least 3 days.

50. (Previously amended) A liquid formulation of a taxane according to claim 49, wherein said taxane concentration is at least 5.0 mg/ml.

51. (Previously amended) A liquid formulation of a taxane according to claim 49, wherein said taxane concentration is at least 10.0 mg/ml.

52. (Previously amended) A drug formulation suitable for administration of drug to a subject in need thereof by inhalation or oral administration, said formulation comprising at least one protein and drug nanoparticles having a size of about 10-1,000 nm, plus optionally an excipient.

53. (Reiterated) A method of making nanoparticles containing an active agent, said method comprising:

a) combining a non-volatile phase, a volatile phase, and a surfactant that spontaneously form a microemulsion, wherein said volatile phase contains said active agent; and

b) removing said volatile phase and thereby obtaining a suspension of solid nanoparticles in said non-volatile phase, wherein said nanoparticles contain said active agent and have an average diameter of less than 100 nm.

54. (Reiterated) A method according to claim 53, wherein said nanoparticles have an average diameter of less than 50 nm.

55. (Reiterated) A method according to claim 53, wherein said microemulsion further comprises a cosurfactant.

56. (Reiterated) A method according to claim 53, further comprising:

c) removing said surfactant and/or cosurfactant by dialysis, ultrafiltration, or adsorption.

57. (Reiterated) A method according to claim 53, further comprising:

c) removing essentially all of the remaining non-volatile phase by freeze-drying, spray-drying, or lyophilization, so as to obtain a dry powder of nanoparticles.

58. (Reiterated) A method according to claim 57, further comprising:

d) resuspending said dry powder of nanoparticles in a pharmaceutically acceptable carrier.

59. (Reiterated) A method according to claim 58, further comprising:

e) administering said resuspended nanoparticles to a patient.

60. (Reiterated) A method according to claim 53, further comprising:

c) filtering said suspension of solid nanoparticles through a filter of sufficiently small pore size so as to sterilize said suspension.

61. (Reiterated) A method of making nanoparticles containing an active agent, said method comprising:

a) combining a non-volatile phase and a volatile phase that spontaneously form a microemulsion, wherein said non-volatile phase contains said active agent; and

b) removing said non-volatile phase and thereby obtaining solid nanoparticles in said volatile phase, wherein said nanoparticles contain said active agent and have an average diameter of less than 100 nm.

62. (Reiterated) A suspension of nanoparticles made by the method of claim 53.

63. (Reiterated) Dry nanoparticles made by the method of claim 57.

64. (Reiterated) A suspension of nanoparticles made by the method of claim 58.

65. (Reiterated) A suspension of nanoparticles made by the method of claim 61.

66. (Reiterated) A dry powder formulation of a taxane suitable for administration of a taxane to a subject in need thereof upon reconstitution, wherein said formulation is substantially free of surfactants.

67. (Reiterated) A dry powder formulation of a taxane suitable for administration of a taxane to a subject in need thereof upon reconstitution, wherein said formulation is substantially free of cremophor.

70. (Reiterated) A lyophilized formulation suitable for administration of a taxane to a subject upon reconstitution, wherein said formulation comprises taxane nanoparticles whose size remains substantially constant prior to and after reconstitution.

71. (Reiterated) An article of manufacture comprising a sealed vial containing a dry powder formulation of a taxane, wherein said formulation comprises taxane nanoparticles having an average diameter in the range of about 10 nm up to about 8 μm.

72. (Amended) An article of manufacture according to claim 71, wherein said formulation is stable for at least 3 days.

73. (Reiterated) An article of manufacture comprising a dry powder or liquid formulation of drug and at least one protein, wherein said formulation comprises drug nanoparticles that have been filtered through a sterilizing filter.

74. (Reiterated) An article of manufacture according to claim 73 wherein said drug is a taxane.

75. (Amended) An article of manufacture according to claim 74, wherein said liquid formulation of taxane is free of surfactants.

76. (Reiterated) The method of claim 35 wherein said rate is between 6-16 $mg/m^2/min$.

77. (Reiterated) The method of claim 35 wherein said taxane is used to treat cancer in said human subject.

78. (Reiterated) The method of claim 35 wherein said taxane is used to treat vascular restenosis in said human subject.

79. (Amended) The formulation of claim 46 wherein said nanoparticles have a mean particle size in the range of about 29 nm up to about 400 nm.

80. (Amended) The formulation of claim 46 wherein said dry powder formulation of taxane is suitable for the treatment of tumors in the brain or peritoneal cavity.

81. (Reiterated) A liquid formulation of a taxane according to claim 49, wherein said taxane concentration is at least 20 mg/ml.

82. (Reiterated) A method for the administration of a taxane to a human subject in need thereof, said method comprising systemically administering said taxane to said subject at a concentration of at least 2 mg/ml.

83. (Reiterated) The method of claim 82 wherein said concentration of said taxane is at least 5 mg/ml.

84. (Reiterated) The method of claim 82 wherein said concentration of said taxane is at least 10 mg/ml.

85. (Reiterated) The method of claim 82 wherein said concentration of said taxane is at least 20 mg/ml.

86. (Amended) The formulation of claim 52 wherein said drug nanoparticles are contained within protein microparticles having a size of about 1-10 μm.

87. (Reiterated) The formulation of claim 52 wherein said drug formulation may be used in conjunction with oral bioavailability enhancers.

88. (Reiterated) An article of manufacture comprising a drug formulation in a sealed vial suitable for administration of a drug to a human subject in need thereof, said formulation comprising at least one protein and drug nanoparticles having a size in the range of about 10 nm up to about 1000 nm.

89. (Amended) The article of claim 88 wherein said drug formulation is a dry powder.

90. (Amended) The article of claim 88 wherein the drug formulation is a liquid.

91. (Amended) The article of claim 88 wherein said drug is hydrophobic.

92. (Reiterated) A formulation of paclitaxel suitable for administration to a human subject in need thereof wherein the pharmacokinetics are such that the area under the curve (AUC) for paclitaxel in said formulation is significantly less than the AUC for paclitaxel in TAXOL at the same dose.

93. (Reiterated) A formulation of paclitaxel suitable for administration to a human subject in need thereof wherein the pharmacokinetics are such that half-life for paclitaxel in said formulation is significantly higher than the half-life for paclitaxel in TAXOL at the same dose.

94. (New) A formulation according to claim 49 wherein said formulation further comprises one or more of albumin, a polyalkylene glycol, or an oil.

95. (New) A formulation according to claim 94 wherein said oil is an oil-soluble vitamin.

96. (New) A formulation according to claim 95 wherein said vitamin is vitamin A, vitamin D, vitamin E or vitamin K.

97. (New) A formulation according to claim 49 wherein said taxane is non-crystalline.

98. (New) A formulation according to claim 52 wherein said protein is albumin.

99. (New) A formulation according to claim 52 wherein said formulation is solid or liquid.

100. (New) A method according to claim 61 wherein said active agent is selected from the group consisting of an anti-neoplastic, an anesthetic and a hormone.

101. (New) An article of manufacture according to claim 73 wherein said protein is albumin.

102. (New) An article of manufacture according to claim 73 wherein said formulation is solid or liquid.

103. (New) An article of manufacture according to claim 73 wherein said drug is selected from the group consisting of an anti-neoplastic, an anesthetic and a hormone.

104. (New) An article of manufacture according to claim 103 wherein said anti-neoplastic is a taxane.

105. (New) An article of manufacture according to claim 103 wherein said anesthetic is propofol.

106. (New) An article of manufacture according to claim 103 wherein said hormone is a thyroid hormone.

107. (New) A formulation according to claim 73 wherein said drug is non-crystalline.

108. (New) A formulation according to claim 73 wherein said nanoparticles are suitable for administration to a subject by oral, topical, ocular, intramuscular, intravenous, intraperitoneal, intraarterial, intraurethral, intrathecal, or inhalation administration

109. (New) An article of manufacture according to claim 88 wherein said formulation is solid or liquid.

110. (New) An article of manufacture according to claim 88 wherein said drug is selected from the group consisting of an anti-neoplastic, an anesthetic and a hormone.

111. (New) An article of manufacture according to claim 110 wherein said anti-neoplastic is a taxane.

112. (New) An article of manufacture according to claim 110 wherein said anesthetic is propofol.

113. (New) An article of manufacture according to claim 110 wherein said hormone is a thyroid hormone.

114. (New) An article of manufacture according to claim 88 wherein said drug is non-crystalline.

115. (New) A formulation according to claim 92 further comprising one or more of albumin, a polyalkylene glycol, and an oil.

116. (New) A formulation according to claim 115 wherein said oil is an oil-soluble vitamin.

117. (New) A formulation according to claim 115 wherein said vitamin is vitamin A, vitamin D, vitamin E or vitamin K.

118. (New) A formulation according to claim 92 wherein said paclitaxel is non-crystalline.

119. (New) A formulation according to claim 93 further comprising one or more of albumin, a polyalkylene glycol, and an oil.

120. (New) A formulation according to claim 119 wherein said oil is an oil-soluble vitamin.

121. (New) A formulation according to claim 119 wherein said vitamin is vitamin A, vitamin D, vitamin E or vitamin K.